

Amendments to the Specification:

Please amend the specification as shown:

Please delete the paragraph on page 10, lines 7-19 and replace it with the following paragraph:

Further convertase inhibitors suitable for use according to the invention include:

- (i) alpha 1-antitrypsin (α -1 PDX), or nucleic acids encoding the same;
- (ii) derivatives of alpha 1-antitrypsin such as those comprising the amino acid sequences arg-val-pro-arg (**SEQ ID NO: 4**), ala-val-arg-arg (**SEQ ID NO: 5**) or arg-val-arg-arg (**SEQ ID NO: 6**), or nucleic acids encoding the same;
- (iii) p-chloromercuribenzoate;
- (iv) tosylamido-phenylethyl chloromethyl ketone (TPCK);
- (v) D-polyarginines (e.g. hexa-arginine (**SEQ ID NO: 7**) and its derivatives);
- (vi) Acetyl-leu-leu-arg-aldehyde hemisulfate;
- (vii) S-carboxyphenylethyl-carbamoyl-arg-val-arg-aldehyde;
- (viii) Threodimercaptobutanediol; and
- (ix) Tos-Lys-chloromethylketone.

Please delete the paragraph on page 11, lines 8-16 and replace it with the following paragraph:

The surprising finding that extracellular convertase activity contributes to TGF- β activation led the inventors to realise that water-soluble convertase inhibitors may be used to decrease TGF- β activation, and thus reduce scarring. The use of water-soluble inhibitors, which cannot penetrate the cell membrane, is particularly advantageous since such inhibitors generally exhibit low levels of cytotoxicity. Water-soluble convertase inhibitors can also be readily formulated into compositions that induce minimal inflammatory reactions, an

important consideration when designing anti-scarring agents. A preferred water-soluble convertase inhibitor suitable for use according to the invention is L-hexaarginine (SEQ ID NO: 7).

Please delete the paragraphs on page 21, line 21 to page 22, line 7 and replace them with the following paragraphs:

Figure 1 illustrates the results of analysis of the ability of different inhibitors, and putative inhibitors, of TGF- β activation to prevent TGF- β activation by platelets. **'LSKL' is disclosed as SEQ ID NO: 8 and 'dec-RVKR-cmk' is disclosed as SEQ ID NO: 1;**

Figure 2 illustrates the effect of Dec-RVKR-cmk (SEQ ID NO:1) and hexaarginine (SEQ ID NO: 7) in: **A** platelet releasates; and **B** platelet-free releasates as referred to in experimental results section 2 of the example. In **A** ■ indicates active hexaarginine (SEQ ID NO: 7) and □ indicates total hexaarginine (SEQ ID NO: 7) whereas ● indicates active dec-RVKR-cmk (SEQ ID NO:1) and ○ indicates total dec-RVKR-cmk (SEQ ID NO:2). In panel **B** ○ indicates hexaarginine (SEQ ID NO: 7) whereas ● indicates dec-RVKR-cmk (SEQ ID NO:1); and

Figure 3 illustrates the effect of furin inhibitors on furin activity in cell lysates and releasates for control samples (■); dec-RVKR-cmk (SEQ ID NO:1) (▣) ; and hexaarginine (SEQ ID NO: 7) (◻) in experimental results section 2 of the example.

Please delete the paragraph on page 25, line 21 to page 26, line 2 and replace it with the following paragraph:

The results showed that latent TGF- β activation was not significantly affected by the presence of inhibitors specific for TSP-1 (LSKL peptide (SEQ ID NO: 8)), plasmin (neutralising monoclonal antibody, PG19 - a neutralising antibody provided by Dr. Michael Kramer), or M6P/IGF-II receptor (M6P - mannose-6-phosphate) (panel A). Moreover, a number of inhibitors (aprotinin, pefabloc, α 1-antitrypsin, E-64, pepstatin, leupeptin, caspase-

3 inhibitor and calpain inhibitor) of other proteinases potentially involved in platelet-mediated latent TGF- β activation also proved to be ineffective (panel *B*).

Please delete the paragraphs on page 27, lines 4-18 and replace them with the following paragraphs:

Platelets were activated with thrombin in the absence or presence of furin inhibitors. Platelets were pre-incubated with hexaarginine (**SEQ ID NO: 7**), whereas dec-RVKR-cmk (SEQ ID NO:1) was added 5 min after thrombin addition because of interference with platelet activation at higher concentrations. Active and total TGF- β in releasates were determined in the PAI/L bioassay. The results are shown in panel A of Figure 2. Active TGF- β levels in the controls were 82 pg/ml (dec-RVKR-cmk (SEQ ID NO:1) data) and 61 pg/ml (hexaarginine (**SEQ ID NO: 7**) data), total TGF- β levels were 33.4 ng/ml (dec-RVKR-cmk (SEQ ID NO:1) data) and 39.5 ng/ml (hexaarginine (**SEQ ID NO: 7**) data).

In a further experiment, furin inhibitors were added to platelet-free releasates of activated platelets, and activation was allowed to continue in the absence of platelets for 30 min at 37°C. The results of this experiment are shown in panel B of Figure 2. Active TGF- β levels in the controls were 77 pg/ml (dec-RVKR-cmk data (SEQ ID NO:1)) and 104 pg/ml (hexaarginine data (**SEQ ID NO: 7**)). Incubation on ice reduced activation in the controls to approximately 56% (data not shown). Data represent the mean values of three independent experiments assayed in triplicate.

Please delete the paragraphs on page 27, line 25 to page 28, line 23 and replace them with the following paragraphs:

The most prominent and ubiquitously expressed member of this endoprotease family is furin, which typically cleaves at the consensus sequence motif R-X-(K/R)-R. The membrane-impermeable furin inhibitor, hexa-L-arginine (**SEQ ID NO: 7**), also significantly reduced active TGF- β in releasates (Fig. 2 panel A) indicating that at least part of the activation occurred extracellularly following latent TGF- β release.

Latent TGF- β activation appeared to be enzymatic and independent of the continuous presence of platelets, since incubation of platelet-free releasates on ice (as compared to 37°C) reduced active TGF- β levels to approximately 56%. As observed for platelet suspensions, activation in releasates was inhibited, in a dose-dependent fashion, by the furin inhibitors, dec-RVKR-cmk (SEQ ID NO:1) and hexa-L-arginine (SEQ ID NO: 7) (Fig. 2B). This indicates that the furin-like enzyme involved in latent TGF- β activation is released from activated platelets.

3. 2. Platelets contain and release furin-like enzyme activity.

Releasates or hypotonic lysates of activated platelets were assayed using the furin substrate, pyr-RTKR-amc (SEQ ID NO:3) in the absence or presence of the furin inhibitors, hexaarginine (SEQ ID NO: 7) (200 μ M) or dec-RVKR-cmk (SEQ ID NO:1) (150 μ M). Values were corrected for substrate-independent endogenous fluorescence (control without substrate) as well as for spontaneous substrate hydrolysis (buffer control). Mean values \pm S.E.M. of 2-3 separate experiments assayed in duplicate are shown.

The presence of furin-like enzyme activity in both hypotonic lysates and releasates of human platelets was analysed using the fluorogenic furin substrate, pyr-RTKR-amc (SEQ ID NO:3). Platelet lysates contained a furin-like enzyme activity, part of which (approximately 12%) was released upon thrombin stimulation. Enzyme activity in cell lysates and releasates was inhibited by dec-RVKR-cmk (SEQ ID NO:1) and hexa-L-arginine (SEQ ID NO: 7) (Fig. 3).

Please delete the paragraph on page 29, lines 10-23 and replace it with the following paragraph:

In summary, the inventors found that platelets are not only major storage sites for latent TGF- β 1 but also activate part of it following degranulation. While the mechanism of activation does not require any of the well-characterized activators, TSP-1, M6P/IGF-II receptor, or plasmin, the platelet latent TGF- β complex appears to be activated via a sequence of events by a furin-like convertase released by the platelets. Following release *in vivo*, this enzyme appears to continue to operate, independently of the presence of platelets, in the

surrounding tissue (e.g. the wound area), leading to the activation of extracellular-matrix associated latent TGF- β complex. Therefore, this novel mechanism of activation represents a target to modulate TGF- β activity in pathologic conditions involving platelet degranulation, such as wound repair, fibrosis, arteriosclerosis, and cancer. Therefore the inventors have found that inhibitors according to the invention (such as decanoyl-RVKR-cmk (SEQ ID NO:1) and hexa-arginine (**SEQ ID NO: 7**) may be used according to the invention).